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Comparison of the effects of methadone and butorphanol combined with acepromazine for canine gastroduodenoscopy

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Abstract

Objective To evaluate the feasibility of gastroduodenoscopy in dogs premedicated with acepromazine in combination with butorphanol or methadone.

Study Design Prospective, randomized double-blinded clinical trial

Animals A total of 40 client-owned dogs

Methods: Dogs were randomly allocated to be given intramuscular acepromazine 0.02 mg kg^{-1} combined with either butorphanol 0.3 mg kg^{-1} (ACEBUT) or methadone 0.2 mg kg^{-1} (ACEMET). General anaesthesia was induced with propofol and ketamine and maintained with sevoflurane (FE'Sevo 2.3 %) in oxygen. Cardiopulmonary variables were recorded at 5-minute intervals during anaesthesia. Feasibility of the entire gastroduodenoscopy was evaluated with a visual analogue scale (VAS) from 0 (best) to 100 (worst) (primary outcome of the study). Lower oesophageal sphincter dilatation and duodenal intubation were scored. Pylorus diameter was measured with standard endoscopic inflatable balloons. Overall cardiovascular stability VAS (0 - 100) was assessed after anaesthesia as was the presence of fluid in the oesophagus, regurgitation, need for mechanical ventilation, and intra- and postoperative rescue analgesia (secondary outcomes of the study). Differences between treatments were analysed with Mann-Whitney U, student t-test, Fisher Exact test or mixed model analysis of variance as appropriate. Subsequently, feasibility VAS of the gastroduodenoscopy was assessed for non-inferiority between treatments. The non-inferiority margin was set as -10.

Results: All gastroduodenoscopies were successfully completed with both treatments using an endoscope tip diameter of 12.8 mm in all but one dog. Feasibility of

gastroduodenoscopy was evaluated as 2.9 ± 5.6 with ACEBUT and 5.1 ± 5.8 with ACEMET. No significant differences between treatments were detected in any measured or assessed variables, and non-inferiority was confirmed.

Conclusion and clinical relevance: In our population, the effects of methadone and butorphanol when combined with acepromazine, were comparable.

Keywords acepromazine, butorphanol, dog, gastroduodenoscopy, methadone

Introduction

In human medicine, the provision of sedation and analgesia has been a source of ongoing discussioncritical, when performing gastrointestinal endoscopic procedures, with increasing complexity over the last decade. It has been recognized that the procedures create some pain and discomfort and are associated with anxiety for the human patient. Post-procedural pain has been reported as the second-most frequent adverse event related to gastroduodenoscopy (Goudra et al., 2017).

In veterinary medicine, it is currently deemed impossible to perform upper gastrointestinal endoscopy without general anaesthesia. However, anaesthetic drugs and the stress related to anaesthesia can elicit pre- and post-operative vomiting and alter or impair intestinal motility and sphincter function (Weil, 2009). A comparative experimental study performed in dogs showed that the combination of atropine and morphine, the prototypical μ- agonist used for premedication, resulted in increased difficulty in traversing the pyloric sphincter (Donaldson et al., 1993). These results lead to the generic suggestion that μ-agonists should be avoided when duodenoscopy is performed. More recent investigations in cats suggested no significant difference between hydromorphone (a μ-agonist opioid) and butorphanol (a μ-antagonist, κ-agonist) when gastroduodenscopy was performed (Smith et al., 2004.) In human medicine, fentanyl, a potent μ-agonist, is extensively used in combination with midazolam to provide profound sedation during endoscopy (Lichtenstein et al., 2008) and a combination of remifentanil and propofol seemed to be well tolerated and effective in preventing the gag reflex (Borrat et al., 2015).

Nonetheless, a recent study in dogs concluded that butorphanol enabled easier passage of the endoscope through the pylorus when compared to methadone

(McFadzean et al., 2017). However, the analgesia provided by butorphanol is mild and short in duration. Therefore, the use of methadone, a μ- agonist with dose-dependent sedative properties, which does not induce vomiting after anaesthesia (Monteiro et al. 2008; 2009; Bitti et al. 2017) should be evaluated for this purpose. Moreover, methadone also has N-methyl-D-aspartate (NMDA) receptor antagonist properties and it has been reported that NMDA antagonism selectively inhibits the oesophageal component of transient lower oesophageal sphincter (LOS) relaxation (Lehmann and Bränden, 2001).

In dogs, methadone alone induced mild sedation while the combination of methadone and acepromazine produced mild to intense sedation with minimal cardiopulmonary effects (Monteiro et al. 2008). The combination of methadone and acepromazine has not been compared with the combination of butorphanol and acepromazine when ease of gastroduodenscopy is assessed in dogs. Therefore, this study aimed to compare the effect of butorphanol *versus* methadone, when combined with acepromazine, on 1) the feasibility of gastroduodenoscopy and 2) gastrointestinal effects during and after endoscopy. We hypothesized that the combination of methadone and acepromazine would be non-inferior to the combination of butorphanol and acepromazine.

Material and methods

The study obtained ethical approval from the Research Ethics Committee of the University of Helsinki, Finland (Statement 6/2017). Informed owner consent was obtained for each dog enrolled in the study.

Animals

A group of 40 client-owned dogs scheduled for gastroduodenscopy, were included in the study. Specifically, middle- to large-sized dogs of American Society of Anesthesiologists (ASA) status scores I or II according to clinical and laboratory examinations, without previous signs of other diseases than gastro-intestinal. These animals were involved in a parallel study assessing the diagnostic value of chromoendoscopy in gastroenterology (Statements 5/2015 and 6/2017 of Research Committee of the University of Helsinki, Finland). Exclusion criteria were: intraoperative administration of anticholinergic agents or the unexplained finding of a full stomach after fasting. Sample size was computed with G*Power software (Heinrich-Heine University, Germany), aimed at a difference in the feasibility of the procedure between groups acepromazine and butorphanol (ACEBUT) and acepromazine and methadone (ACEMET). Evaluations were performed by the same observer using a visual analogue scale (VAS). A minimum of 26 animals were needed to be 80% sure that the lower limit of a one-sided 95% confidence interval was above the non-inferiority limit of -10, if no true difference among the groups was found. The margin of non-inferiority limit was based on a VAS difference representative of a significant clinical difference.

Study protocol

The study was organized as prospective, randomized, double-blinded, clinical trial. Data collection started on April 2017 and ended on August 2018. Each endoscopic procedure was performed by a single experienced endoscopist (MC); anaesthesia was performed by an anaesthesiologist (DC) or an anaesthetist well-accustomed with the procedures (JL). Dogs enrolled in the study were randomly assigned (ratio 1:1, two blocks to two groups: ACEBUT or ACEMET (www.randomization.com by Gerard E. Dallal, PhD). Dogs in

105 the ACEBUT group were premedicated with intramuscular acepromazine (Plegicil 10 mg
106 mL^{-1}, Bela-Pharm GmbH, Germany) 0.02 mg kg^{-1} and butorphanol (Torbudor 10mg mL^{-1}
107 , Richter Pharma AG, Austria) 0.3 mg kg^{-1}, whereas the dogs assigned to ACEMET were
108 given acepromazine 0.02 mg kg^{-1} and methadone 0.2 mg kg^{-1} (Synthadon vet 5 mg mL^{-1},
109 Le Vet Beheer B.V, the Netherlands).

110 Food was withheld at least for 14 hours prior to general anaesthesia for
111 complete gastroduodenal emptying and adequate mucosal examination during
112 gastroduodenoscopy (De Cuyper et al., 2018). Water was available until 2 hours before
113 the procedure.

114 After admission to the hospital, dogs were allowed to acclimatize to the
115 environment and the personnel before premedication. Premedication drugs were mixed
116 in a single syringe covered with tape and labelled as "premedication", so that the content
117 was obscured. Both the endoscopist and the person in charge of the anaesthesia remained
118 unaware of group allocation. After injection, dogs were left undisturbed in the room but
119 observed for signs of adverse reactions.

120 After 20 minutes, the level of sedation was assessed using a composite
121 sedation scale ranging from 0 (no sedation) to 21 (strongly sedated) (adapted from Young
122 et al., 1990 and modified from Girard et al., 2010) (Appendix A1). Thereafter, a 20-gauge
123 catheter (Terumo Europe N.V, Belgium) was placed into a cephalic vein and crystalloids
124 infusion was started at rate of 5 mL kg^{-1} $hour^{-1}$ (Ringer-Acetat, Baxter Viaflo, IL, USA).
125 Lead II monitoring of the electrocardiogram (ECG) and non-invasive blood pressure
126 measurement was also initiated at this time. After 5 minutes of pre-oxygenation with
127 untighten face mask (oxygen flow 2 L $minute^{-1)}$, general anaesthesia was induced with 1
128 mg kg^{-1} of ketamine intravenously (IV) (Ketaminol vet 50 mg mL^{-1}, Intervet

129 International, the Netherlands) followed by slow administration of propofol (Vetofol vet
130 10 mg mL^{-1}, Norbrook Laboratories Limited, UK) to effect, starting with a dose of 2 mg
131 kg^{-1} administered IV. Once unconsciousness was achieved, the trachea was intubated with
132 a silicone cuffed endotracheal tube (Mila International Inc., KY, USA, internal diameter
133 11-12 mm) and connected to a circle breathing system (Matrx VMS, Midmark
134 Corporation, OH, USA). General anaesthesia was maintained with sevoflurane
135 (Sevorane, Aesica Queenborough Ltd, UK), in 100% oxygen targeting a 2.3 % (1 MAC)
136 (Kazama & Ikeda, 1988) end-tidal concentration of sevoflurane (F_E'Sevo) during
137 gastroduodenoscopy. Dogs were positioned in left lateral recumbency for
138 gastroduodenoscopy. Heart rate (HR) by means of continuous lead II ECG, haemoglobin
139 oxygen saturation (SpO_2), respiratory rate (f_R**),** inspiratory oxygen fraction (F_IO_2), end-
140 tidal carbon dioxide ($P_E'CO_2$) and F_E'Sevo, and rectal temperature were monitored
141 continuously and recorded every 5 minutes throughout the procedure. Oscillometric non-
142 invasive blood pressure was monitored every 2.5 minutes and recorded every 5 minutes
143 with multiparametric monitor (BSM-2301K, Nihon Kohden, Japan). The respiratory gas
144 monitor (Capnomac Ultima, Datex-Ohmeda, , Finland) was calibrated before every trial
145 with a calibration gas supplied by the manufacturer (Quick Cal Calibration Gas, GE
146 Healthcare, Finland).

147 Hypotension was defined as mean arterial pressure (MAP) below 60
148 mmHg. The following actions were planned as subsequent steps, to treat hypotension:
149 crystalloid fluid bolus at 5 - 10 mL kg^{-1} IV, colloid bolus at 2 mL kg^{-1} (Voluven, Fresenius
150 Kabi, Sweden) and ephedrine at a dose of 0.1 mg kg^{-1} IV (Efedrin Stagen 3 mg mL^{-1},
151 Stagen Nordic A/S, Denmark).

At 5 minutes before the start of endoscopy, mean arterial pressure (MAP), HR and f_R were recorded as baseline values. If two out of the three variables, HR, f_R or MAP, increased more than 20% from baseline during the procedure, 3 μg kg^{-1} of fentanyl (Fentanyl-Hameln 50 μg mL^{-1}, Hameln Pharma Plus Gmbh, Germany) was given IV. The need of intra-operative fentanyl was recorded (Yes/No).

The endoscopes used were either a gastroscope with 9.9 mm tip diameter and 103 cm tube length (GIF-H180J, Olympus Exera II, Olympus Europa, Germany) or a colonoscope with 12.8 mm tip diameter and 133cm tube length (CFQ180AL, Olympus Exera II, Olympus Europa, Germany). For each endoscopy the tip diameter of the endoscope with which the pylorus was traversed was recorded (9.9 or 12.8 mm). Carbon dioxide was used for insufflation of the gastrointestinal tract. The endoscopist, who was blinded to the allocated group, evaluated each animal for the presence of fluid in the oesophagus (Yes/No), and the relaxation of LOS (none; mild; moderate; marked). A stopwatch of the mobile phone (Nokia, 3310, Finland) was used to record the time between closely visualizing the pyloric sphincter and achieving a tubular image of the proximal duodenum. The score of the procedure for pyloric intubation was graded by the endoscopist using 4-point scale as 1) no resistance to pass through the pylorus; 2) minor resistance; pylorus passed at the first attempt; 3) two or more attempts needed to pass the pylorus; and 4) duodenum not reached (modified from Matz et al. 1991). The diameter of the pyloric sphincter was then estimated by passing calibrated balloon catheters through the pylorus (M00558470, M00558480 or M00558490, Boston Scientific International SA, France). Each attempt started at maximum inflation and pyloric diameter was recorded for the balloon, which passed through the sphincter.

During general anaesthesia, the dogs were allowed to breath spontaneously. Cut-off value for providing mechanical ventilation (Hallowell EMC Model 2002IE^{Pro}, Hallowell EMC, MA, USA) was set at $P_{E´}CO_2$ of 55 mmHg (7.3 kPa).

At the end of general anaesthesia, dogs were disconnected from the anaesthetic system and recovered in the same room under the supervision of the anaesthetist (DC or JL). SpO_2 was monitored continuously and oxygen was supplied via facial mask before and after the tracheal extubation and until the dogs achieved sternal recumbency. After completing the gastroduodenoscopy, general feasibility of the procedure was evaluated by the endoscopist and cardiovascular stability by the anaesthetist with visual analogue scales (VAS, 0 - 100), where 0 represented the most feasible gastroduodenoscopy or the most stable cardiovascular function, whereas 100 indicated unsuccessful gastroduodenoscopy procedure or administration of atropine due to the a sudden decrease in HR. Post-operative pain was evaluated 1 hour after tracheal extubation with the short form of Glasgow composite pain scale (GCPS) (Reid et al. 2007) and recorded; metamizole 25 mg kg^{-1} (Litalgin 500/2 mg mL^{-1}, Takeda Austria GmbH, Austria), was administered as rescue analgesia given IV (GCPS $\geq$ 6/24). Dogs were discharged when able to walk normally, oriented, and responded to handling and verbal stimuli from researchers and owners as before anaesthesia.

The day following the endoscopic procedure the owners were contacted for a short telephonic questionnaire (Appendix A2).

Statistical analysis

All data were analysed using SPSS software (IBM SPSS Statistics for Windows, version 25, IBM Corp., NY, USA) and a $p \leq 0.05$ was considered statistically significant. The

data were tested for distribution of normality with Shapiro-Wilk's test. Differences between treatments were tested with Student t-test (normal variables) and Mann-Whitney U test (non-normal variables). Categorical variables were analysed with Fisher Exact test. Repeatedly recorded cardiopulmonary variables were analysed with mixed model of analysis of variance (ANOVA) with *post-hoc* Bonferroni correction at selected time points, *i.e.* just before starting gastroduodenoscopy, at the time of passing duodenum, and at 60, 90 and 120 minutes from premedication. Parametric continuous data are presented as mean ± standard deviation (SD), and nonparametric continuous and categorical data as median (minimum - maximum). Non-inferiority of ACEMET to ACEBUT was claimed if the lower limit of the 95% of confidence interval (CI) for the difference in mean feasibility of gastroduodenoscopy (VAS) was greater than -10. This test for non-inferiority was only performed for the primary outcome variable (feasibility of gastroduodenoscopy) if superiority was not demonstrated between treatments; all other variables were tested for superiority of ACEBUT versus ACEMET.

Results

Data from 37dogs were analysed, of which 20 belonged to ACEBUT and 17 to ACEMET group. Of the initial 40 dogs, three dogs were excluded from further analysis as gastroduodenoscopy was aborted owing to a full stomach. A further 2 dogs with signs of upper gastrointestinal disease (one dog in each group) were euthanized immediately after the gastroduodenoscopy, due to severe gastric and duodenal changes compatible with neoplasia later histologically diagnosed as carcinoma. The post-operative data collection was therefore performed in 35 dogs.

Of the 37 dogs included in the analysis, 33 were Belgian shepherd dogs; two were Labrador retrievers; one was a Golden retriever and one was a Rhodesian ridgeback. Mean body weight was 25.9 ± 6.0 kg and 25.4 ± 5.3 kg for ACEBUT and ACEMET, respectively. Mean age of the dogs was 8.7 ± 2.3 years (ACEBUT) and 9.4 ± 1.7 years (ACEMET). There were no significant differences between groups in either weight or age. Among dogs with overt upper gastrointestinal disorders (ASA 2), 13 were premedicated with ACEBUT and 12 with ACEMET. Among ASA 1 dogs, seven were premedicated with ACEBUT and five with ACEMET.

Gastroduodenoscopies were successfully completed in 36/37 dogs with a 12.8-mm endoscope. On one occasion, a 9.9-mm endoscope was used.

Sedations scores assessed 20 minutes after administration of premedication, were 11.5 (7 - 16) for ACEBUT and 11 (5 - 18) for ACEMET (p = 0.752). The time between the premedication and the start of the gastroduodenoscopy was 48 (37 - 66) minutes for ACEBUT and 48 (38 - 79) minutes for ACEMET (p = 0.59).

No differences between groups were detected in the following variables: presence of fluid in oesophagus, LOS dilatation, need for mechanical ventilation or regurgitation during the anaesthesia (Table 1). Intraoperative rescue analgesia was needed in 10/20 dogs with ACEBUT and 6/17 dogs with ACEMET (p = 0.51). 3 dogs given ACEBUT and 2 dogs given ACEMET needed more than one bolus of fentanyl. The intraoperative rescue analgesia was administered shortly after the start of gastroduodenoscopy in five/10 given ACEBUT and in two/six given ACEMET (p = 0.63).

Duodenal intubation was achieved in all dogs (detailed results are shown in Table 1). The time to reach the duodenum was 32.5 ± 30.4 seconds in the ACEBUT

group and 47.8 ± 32.9 seconds in the ACEMET group (p = 0.168). The diameter of the pylorus was 16 (13 - 18) mm and 15 (13 - 18) mm in the ACEBUT and ACEMET groups respectively (p = 0.46).

VAS scores of gastroduodenoscopy feasibility were not different between the two groups (detailed results are shown in the Table 2). The lower limit of 95% CI of the difference for gastroduodenoscopy feasibility VAS was greater than the set margin for non-inferiority (-10), thus confirming non-inferiority of ACEMET versus ACEBUT.

The results of cardiovascular stability VAS were not different between treatments (Table 2). Mild hypotension was detected in six/37 dogs and managed with crystalloid boluses. No dog required further treatment for hypotension. No anticholinergic drugs were administered. Detailed results from the selected time points of HR, MAP and f_R are presented in the Table 3. HR at the time of traversing the pyloric sphincter with endoscope was significantly higher in both groups in comparison to the start of the gastroduodenoscopy and at the 120 minute time point. However, no differences between groups were detected at any analyzed time points. No differences were detected over time or between treatments in MAP and f_R.

At 1 hour after the completion of gastroduodenoscopy, GCPS points were 2 (1 - 6) in the ACEBUT group and 1 (0 - 5) for ACEMET group (p = 0.094). In the ACEBUT group, one dog required post-operative rescue analgesia with IV metamizole. The descriptive results from owners' questionnaire on the day following the procedure are presented in Table 4. According to the owner, nine/20 dogs that were given ACEBUT had gastrointestinal abnormalities during the first 24 hours after the gastroduodenoscopy and two/17 dogs in ACEMET group. All the dogs could walk normally the day after the procedure. The most commonly reported gastrointestinal abnormalities in the 11 dogs

were either no faeces (one/nine and one/two for ACEBUT and ACEMET, respectively) or diarrhoea (three/nine in the ACEBUT group and one/two in the ACEMET group) during the 24 hours following gastroduodenoscopy. Drooling was noticed during the return car journey to the hospital (four/19 with ACEBUT and one/16 with ACEMET). Only one dog given ACEBUT had decreased appetite in the following morning, and none of the dogs vomited.

Discussion

Both premedication regimens resulted in easy gastroduodenoscopy, according to the VAS and none to mild pyloric spasm were detected endoscopically. Our results demonstrate, that the feasibility of gastroduodenoscopy in the ACEBUT group was not superior to ACEMET, and the non-inferiority analysis confirmed the non-inferiority of ACEMET regarding our primary outcome. We selected as our primary outcome the feasibility of the procedure, instead of duodenal intubation, because we wanted to use an holistic evaluation of the effects of premedication on gastroduodenoscopy. The presence of a single experienced endoscopist performing and evaluating all the procedures increases the validity of this study result. Indeed, the level of experience of the endoscopist has been reported to influence the overall feasibility of the procedure (Matz et al., 1991). No clinically or statistically significant differences were detected between groups in any secondary outcome variables. Although the passage of the pylorus was scored as" 0" in a higher number of dogs in the group ACEBUT.

A recent study demonstrated that shorter and easier duodenal intubation was achieved in dogs premedicated with IV butorphanol when compared with methadone alone (McFadzean et al., 2017). Differences in the outcome between that study and the

present one could be due to the combined use of opioids and acepromazine, lower doses of opioids or a different population of dogs in our study. We decided to combine low-dose acepromazine with methadone or butorphanol, in light of their summative effects on the level of sedation to smooth the induction and the maintenance of anaesthesia (Monteiro et al. 2008, Gomes et al. 2018). Sedation scores were not different between the ACEBUT and ACEMET groups when assessed 20 minutes after the IM injection. In the study of Monteiro et al. (2009), methadone combined with acepromazine produced better sedation than a combination of butorphanol and acepromazine. However, higher doses of acepromazine and methadone, and a lower dose of butorphanol in contrast to the current study.

We believe that the combination of acepromazine with opioids for premedication may have contributed to our results in light of the following considerations. Acepromazine produces sedation and tranquilization by blocking central D_2-dopaminergic receptors (Nybäck & Sedvall 1968), whereas the vasodilatory properties of acepromazine are mediated via blocking peripheral α_1-adrenoceptors (Ludders et al., 1983). An earlier study performed in sheep demonstrated that dopamine infusion caused phasic pyloric contractions followed by increased duodenal activity (Ruckebusch & Malbert, 1986). Moreover, antroduodenal stimulation with pyloric closure has been demonstrated after the IV administration of phenylephrine an α_1-adrenoceptor agonist (Ruckebusch & Malbert, 1986). Therefore, we propose that the antagonistic effects of acepromazine on dopaminergic and α_1- adrenergic receptors may reduce gastroduodenal junction motor activity, and thus facilitate gastroduodenoscopy and especially duodenal intubation.

Several receptors, hormones and neurotransmitters are involved in the regulation of gastrointestinal motility. Opioids may have complex effects on both excitatory and inhibitory neural pathways in the gastrointestinal tract, leading to either relaxation or spasm (Holzer 2009). However, gastric emptying is mainly enhanced during parasympathetic activation, while sympathetic activation such as stress, fear, pain, may decrease it and thereby promote pyloric spasm (Jolliffe et al. 2009). In our study population, the anxiolytic properties of acepromazine may also have played an important role in reducing stress and fear and their negative effects on gastrointestinal system, overcoming thus the effect of different opioids.

NMDA-receptor antagonism may also influence gastrointestinal function, as it selectively inhibits the oesophageal component of transient LOS relaxation (Lehmann and Bränden, 2001). Therefore, the combined use of ketamine and methadone, both conferring NMDA-antagonistic properties, could also explain the low percentage of LOS dilatation and gastro-oesophageal reflux (GOR) observed in the group ACEMET. Indeed, most of the dogs given ACEMET for premedication, were scored none or mild LOS dilatation, or fluid in the oesophagus. A previous study (Wilson et al. 2005) reported a higher incidence of GOR in dogs premedicated with acepromazine and morphine in contrast to our study. This discrepancy may relate to either the different methods of GOR assessment *i.e.* direct visualisation in the current study *versus* measurement of oesophageal pH (Wilson et al., 2005); or to the use of morphine, instead of methadone. These opioids share a pure μ-agonism, but not a NMDA antagonism. It is noteworthy that in the study of Wilson et al. (2005), the highest dose of morphine brought about the highest percentage of reflux, pointing out a possible relation between doses of opioids and GOR.

In general, even if gastroduodenoscopy is not considered to elicit severe pain, post-procedural pain is a main concern in human medicine. In our experience, intraoperative nociception was also a concern as several dogs required rescue analgesia. Additionally, similar to the study of McFadzean et al. (2017), increased HR with both treatments were detected at the time of traversing the pylorus. Increased HR could have been related to the nociceptive stimulus or to a change in venous return and subsequent decrease of arterial blood pressure due to the inflated stomach. However, in our study given that the MAP did not change while traversing the pylorus, it might be hypothesized that a nociceptive stimulus and a decrease in venous return occurred. Previous literature suggests that butorphanol may be a less efficacious analgesic when compared to pure μ-agonist opioids (Gades et al. 2000; Taylor et al., 2010; Warne et al., 2013). In our study 10 out of 20 dogs given butorphanol in their premedication regimen needed rescue analgesia during gastroduodenoscopy *versus* 6 out of 17 dogs in ACEMET group. However, significance was not reached. Butorphanol's shorter duration of action (Pfeffer et al., 1980) in comparison to methadone (Ingvast-Larsson et al., 2010) could explain this result. It can also be speculated that the main effects of butorphanol had waned by the time the gastroduodenoscopy procedure started (median time was 48 minutes between premedication and start of endoscopy, in both groups), while the effects of methadone were still present. The combination with acepromazine could also modify the gastrointestinal kinetic properties of both opioids; however, as plasma concentrations of the drugs were not measured in this study, conclusive statements cannot be drawn.

Data were collected from 37/40 dogs in total, which was a higher number of dogs than that indicated by the sample size calculation, *i.e.* 26 dogs. However, this study was conducted in parallel with another study requiring a larger number of dogs. As

the number of the dogs were in line with the approved ethical licence, it was deemed acceptable to include all of these dogs in the statistical analysis. Therefore, the larger sample size could be regarded as a strength of this study.

Our results are derived from a relatively homogenous population of dogs, mainly consisting of middle-aged Belgian shepherds. Belgian shepherds are predisposed to gastric carcinoma (Candido et al., 2018); which is the reason why these dogs were the main breed undergoing gastroduodenoscopy. It is also the reason why symptomatic and asymptomatic dogs with a genetic neoplastic predisposition were included in the study. This homogeneity may have resulted in an immediate selection of the appropriate sized endoscope, which has increases the ease of pyloric intubation in a more heterogeneous group of dogs (Hall, 2015). Unfortunately, previous studies did not specify the diameter of endoscopes used in heterogeneous dog populations (Matz et al., 1991; Donaldson et al., 1993; McFadzean et al., 2017) making such comparisons impossible.

This study have several limitations: we used the short form GCPS for post-procedural pain assessment; however, the scale is meant for the assessment of acute surgical pain. Visceral pain differs from somatic pain, (Gebhart & Bielefeldt, 2016). Therefore, the GCPS may be insufficiently sensitive to differentiate post-operative pain or discomfort. However, the GCPS, is a validated pain scoring tool for assessing acute pain in dogs, and the authors were familiar with its use. Considering the pharmacokinetic and – dynamic properties of butorphanol, administration to a later phase of sedation was an option, thereby avoiding premature waning of its analgesic action. However, this strategy would not have reflected either our clinical routine or the method used to comparing drugs combinations previously. Fentanyl was used for intraoperative rescue analgesia. We decided to administer a short-acting, rapid onset potent analgesic to treat

intraoperative nociception and to avoid any confounding effects of longer acting drugs on our study design. If the autonomic nervous system changes had not been promptly addressed by fentanyl injection, our outcome variables may have been more greatly affected. It is notable that all episodes of intraoperative nociception were corrected with fentanyl. Acepromazine may not be indicated in all dogs necessitating endoscopy, especially if active bleeding is suspected, therefore the validity of our protocol has to be interpreted in light of a population of ASA I and ASA II dogs.

In conclusion, methadone in combination with acepromazine may be a valuable option for premedication in dogs scheduled for gastroduodenoscopy. Further studies are warranted to confirm this result in a more heterogeneous population of dogs and with different evaluators.

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